Successful Immune Moderation Treatment for Progressive Encephalomyelitis with Rigidity and Myoclonus

Shinichi Ueno, Nobukazu Miyamoto, Hideki Shimura, Yuji Ueno, Masao Watanabe, Akito Hayashi, Nobutaka Hattori and Takao Urabe

Abstract

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a rare disease. PERM consists of the same symptoms as stiff person syndrome, in addition to sensory, brainstem and autonomic features. We herein report a case of PERM in a 48-year-old woman who initially presented with spasticity of the lower limbs and subsequently developed upper limb spasticity, perioral myoclonus and restlessness after three months. The onset of potentially fatal dysautonomia was observed at the peak of the disease. Treatment with high-dose immunoglobulin (400 mg/kg, 5 days), levetiracetam and azathioprine resulted in a drastic and sustained improvement of these symptoms. This is an interesting case of PERM in which the patient showed a dramatic improvement following immune moderation.

Key words: progressive encephalomyelitis with rigidity and myoclonus, stiff person syndrome, levetiracetam, intravenous immunoglobulin

(Intern Med 54: 219-221, 2015)  
(DOI: 10.2169/internalmedicine.54.3760)

Introduction

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a rare neurological disorder that was, until recently, classified as a disease belonging to the stiff person syndrome (SPS) spectrum. However, PERM differs from SPS based on the presence of brainstem, autonomic and long tract signs and its usually aggressive course (1). PERM is also characterized by limb and trunk rigidity, painful muscle spasms, hyperekplexia and brainstem involvement (e.g., ocular motor disturbances, dysphagia and dysarthria) (1). In most patients, disease progression occurs subacutely over weeks, and the duration of illness ranges from weeks to years, often with various episodes of exacerbation and remission (2). We herein report the case of a PERM patient who exhibited initial clinical features associated with lower limb rigidity and subsequently developed encephalopathy a few months later before dramatically responding to immunosuppressive therapy.

Case Report

A 48-year-old woman experienced occasional lower limb numbness and low back pain. The following month, she experienced difficulty walking and developed lower limb spasticity. At that time, she was referred to her local hospital, where an extensive investigation was conducted; however, no significant abnormal findings were noted. Soon after, her condition slightly improved with rehabilitation, although her symptoms persisted. Therefore, she was admitted to our hospital in March 2013, presenting with severe stiffness in all limbs, with particularly marked findings in the lower limbs. On a physical examination, dysuria, rigo-spasticity of all limbs, particularly in the lower limbs (the rigo-spasticity improved while sleeping), and generalized hyperreflexia in both feet with extensor plantar responses were observed. There were no sensory disturbances, and the findings of the following examinations were normal: nerve conduction study, MRI of the brain/pelvis, abdominal ultrasonography and routine blood analyses of vitamin B12, the thyroid func-
tion, creatinine kinase, serum antibody-involved autoimmune disease and cerebrospinal fluid (CSF). The examination of the CSF for myelin basic protein and oligoclonal bands was negative. A provisional diagnosis of spastic paraplegia was made, and the patient was discharged in May 2013. Three months later, she was unable to stand without assistance and had to use a wheelchair to visit our hospital. In September 2013, she developed rigo-spatcity and generalized myoclonus without impairment of consciousness and experienced sudden episodes of axial hyperextension after loud sounds. In October 2013, she became unable to stand or walk due to stiffness of the lower extremities and experienced repeated falls at home; therefore, she was readmitted to our hospital. Upon admission, her body weight was 42 kg, her body height was 157 cm, her blood pressure was 97/60 mmHg and her pulse rate was 72/min. We again performed cerebral and cervical MRI and enhanced CT examinations. The findings of blood and CSF analyses were normal (CSF: cell 2/mm$^3$, protein =45 mg/dL, IgG index =0.45) and both antibody-involved autoimmune diseases and onconeural antibodies (GAD, Hu, Yo, Ri, Tr, CV2, Ma2 and amphiphysin) were negative. Following treatment with mir-tazapine as a mood stabilizer, the patient exhibited more frequent and prolonged generalized hyperextension with limb rigidity and myoclonus. A neurological examination demonstrated dysphagia, and clonazepam was administered; however, her condition did not improve. After one week, the patient experienced life-threatening perioral cyanosis and peripheral oxygen desaturation, resulting in cardiac and respiratory arrest. Four minutes later, she was quickly and successfully intubated and ventilated. She was then transferred to the intensive care unit, where she received therapeutic hypothermia and IV methylprednisolone (1,000 mg/day for two days). She showed significant tolerance to midazolam, although her spasticity slightly improved. The features of her disease suggested SPS (1); hence, surface electromyography was performed following extubation, which showed co-contractions in the thigh flexor and extensor muscles, even when she was lying down. Moreover, the stiffness and rigidity dramatically improved with intravenous diazepam (Figure, Supplementary material 1, 2). These observations led to a diagnosis of PERM, and immunotherapy was started. Treatment with IV immunoglobulin (400 mg/kg/d for 5 days), azathioprine (50 mg/day) and levetiracetam (1,000 mg/day) resulted in further improvements in the limb rigidity and myoclonus within one week after the start of therapy, and the patient was consequently able to perform knee extension by herself. However, the lower limb pain persisted, and one month later, she progressively developed anxiety and restlessness. Her mental status gradually worsened, and she experienced suicidal ideation. We therefore started repeat treatment with IV immunoglobulin (400 mg/kg/day for 5 days), and, over the next three days, her condition rapidly improved. Her symptoms subsequently improved periodically during the two months of treatment with levetiracetam, diazepam and azathioprine, and, after three weeks of IV immunoglobulin therapy, she was able to stand by herself (Supplementary material 3).

Discussion

SPS is a rare disorder that typically presents with rigidity, predominantly of the axial and lower limb musculature, and painful muscle spasms (3). The diagnosis of SPS is usually made after excluding other known pathologies, primarily based on the clinical criteria of stiffness with co-contractions of agonist and antagonist muscles and paroxysmal spasms. These features are supported by the findings of various investigations, including neurophysiological examinations, which demonstrate spontaneous motor unit activity at rest simultaneously from both agonist and antagonist muscles (2). PERM includes the same symptoms as SPS, with the addition of sensory, brainstem and autonomic features (2). However, PERM remains an expanding clinical entity that is constantly being enriched with new symptoms and antibodies (4). The heterogeneity of the immunological features of PERM patients suggests that PERM is caused by diverse pathogenic mechanisms in different patients. More recently, a few cases of PERM were found to be associated with anti-glycine receptor antibodies (5-7). Glycine receptors mediate inhibitory neurotransmission, mainly in the caudal pontine brainstem and spinal cord. Such antibodies may disrupt glycnergic inhibition mechanisms, inducing an excessive startle reflex (8). However, the titer of this antibody was not assessed in this case. Carvajal-Gonzalez et al. (9) reported that glycine receptor antibody-positive patients respond well to immunotherapy, in contrast with the findings of earlier studies of this syndrome, which indicated a poor prognosis.

Regarding the treatment of SPS, symptomatic and immunomodulation therapy is usually administered (6). Recently, the efficacy of levetiracetam for the treatment of SPS has been reported (10); the mode of action of this drug includes the facilitation of inhibitory GABAergic transmission. With
respect to immunotherapy, plasmapheresis, intravenous immunoglobulin (IV-Ig), corticosteroids and rituximab have been reported to be successful in individual cases, although the efficacy of these agents has not been established (11, 12). A placebo-controlled, cross-over trial of IV-Ig (2 g/kg body weight per month divided into two daily doses) administered over three months resulted in a decrease in stiffness and improved sensitivity scores in the treatment, but not placebo, group (13). In addition, some reports have demonstrated the efficacy of long-term basement azathioprine treatment for SPS spectrum disorders (6). Most recently, the efficacy of immunotherapy of PERM was reported in 37 glycine receptor-positive patients (9), usually started with a high dose (e.g., 1 mg/kg) of prednisolone and often preceded by intravenous methylprednisolone, followed by plasma exchange or IV-Ig or both; the latter are often repeated and the dose of steroids is generally weaned slowly. Three patients received additional cyclophosphamide, one patient received cyclosporine and two patients received rituximab (one patient as part of lymphoma treatment) before discharge. A few patients are currently on treatment with azathioprine or mycophenolate. These immunotherapies have resulted in good outcomes in these patients (half of the patients exhibited a final modified Ranking scale under 3). Therefore, a previous report (9) concluded that the presence of glycine receptor antibodies may help to identify diseases that respond to immunotherapy, although the above treatments may need to be administered continuously, as relapse may occur and maintenance immunosuppression may be required.

In conclusion, we herein reported a case of successful therapy for PERM with combination treatment consisting of high-dose IV-Ig and levetiracetam followed by azathioprine, which successfully protected the patient against recurrence.

**The authors state that they have no Conflict of Interest (COI).**

---

**References**


© 2015 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html